



Australia



Harvesting biotechnology

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Australia has been a quiet player on the international biotech scene, but in recent years it has been taking strides to reinvent itself as tomorrow's young entrepreneur. This supplement to *Nature* charts that transformation.

The Australian federal government's announcement last month of a ten-year investment programme for research and development (R&D) should please biotech developers. The package includes more than A\$1 billion (US\$700 million) over the next seven years to help bring Australian research discoveries to market. This will merge and supersede several existing programmes, creating a 'one-stop shop' for developers and investors alike to commercialize Australian research discoveries.

The initiative follows a tendency in recent years for the nation's researchers to focus their attention on areas deemed to be of national priority, an agenda set by the government in 2002 (see *Nature* 420, 591; 2002). The Commonwealth Scientific and Industrial Research Organisation (CSIRO) — Australia's largest research body — led the movement, redirecting a third of its budget into six priority areas.

This shift towards applied science has stirred controversy among academics, who tend to advocate pure research, unfettered by commercial pressures. Nonetheless, the consequence will probably be a determined drive by Australian researchers to push discoveries through to application and commercial endpoints.

It will be a tough road to follow, but the nation prides itself on backing 'battlers'. Despite its small population, Australia has a solid reputation in basic research spanning the biomedical, physical and engineering sciences, and makes a notable contribution to the international scientific literature — with one of the highest number of publications per capita in the world.

However, its track record in the biotech marketplace is undeniably weak. The lack of biotech success stories is often attributed to a combination of poor commercial skills in the scientific sector and scant interest from the private investment sector. The level of R&D investment trails below the average for countries in the Organisation for Economic Co-operation and Development (OECD), and the biggest challenge seems to be attracting investors, both domestically and abroad.

But the tide seems to be changing, and this inspired us to produce this supplement to coincide with BIO 2004, the annual convention of the Biotechnology Industry Organization and one of the world's largest biotech meetings. In these pages, a team of science and business journalists profiles core areas where Australia has notable potential because of strong research and unique resources.

For a continent that has long lived off the sheep's back, it is fitting that one of the areas where Australia is likely to see considerable biotech growth is in agriculture, in particular crop enhancement. This sector has enjoyed a long and sustained public investment and the returns are starting to flow in the form of strong research prominence and near-term commercial applications. Growing environmental pressures have also seeded investment into land-management technologies.

More recently, there have been speculative forays in the discovery of natural products, harvesting the fruits of unique ecosystems to generate novel drug leads. And, although Australia's medical biotechnology sector has a comparatively modest standing internationally, early signs indicate that it is learning how to garner sufficient support to take discoveries through the development pipeline to clinical trials.

Finally, being on the doorstep of Asia places Australia in a strategic position for joint ventures and for attracting investment from some of the most rapidly growing economies. There are already well-established educational, political and economic ties between Australia and its regional neighbours. Science offers a bridge between vibrant emerging biotechnology communities.

We are grateful for the support of our advertisers, who made it feasible for us to showcase some of the leading talent in Australia's biotechnology industry. *Nature* carries sole responsibility for all editorial content.

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The Australian biotechnology industry is itching to grow up. Despite decades of world-class discoveries in science, it is a young industry by world standards, and is just starting to find its commercial feet. Charles Beckley reports.

Biotech business Down Under

Australia seems to be holding its breath — waiting for a hugely successful commercial application that will trigger a new phase of growth for its burgeoning biotechnology industry.

Although the sector has strengths in the early research and development stages, it falls down at the commercialization stage. “What’s lacking are mature markets for venture-capital and later-stage investments in biotechnology,” says Michael Panaccio, an investment principal at Starfish Ventures, a small venture-capital firm in Melbourne. But people are now at least starting to think about commercialization and capturing commercial benefits from scientific discoveries.

Public funds channelled through the universities and major government research agencies, such as the Commonwealth Scientific

and Industrial Research Organisation (CSIRO) and the National Health and Medical Research Council, support the bulk of Australia’s early-stage research. “A big advantage here is that our research in biomedical science is strong and well-funded off a low cost base,” says Andy Gearing, chief executive of Biocomm, a Melbourne-based biotech licensing and seed-capital business.

“Good science has traditionally been done in Australia, so we’ve got fairly fertile soil to grow technology companies,” Panaccio says. “There is enough government funding to take the technology out of the universities, set up a company, undertake a few milestones and raise venture money.”

But others say that the federal and state governments could do better. David Beames, chief executive of Virax, a Melbourne

company developing therapies to boost the immune system against a broad range of diseases, believes money could be better spent by putting more resources into fewer enterprises. “Our governments, state and federal, have an aversion to picking winners,” says Beames.

Hedged bets

Mehrdad Baghai, the executive director of business development and commercialization at the CSIRO, agrees: “We have a large amount of research, but it’s spread out. Every state wants to host a biotech cluster. But if the United States has only four major biotech clusters, it would be difficult to argue that Australia should have six or seven. We need to consolidate and specialize.”

Partnerships between government and private companies, such as the Cooperative Research Centres (CRCs), are helping to bridge the gap between Australian science and commercialization. The idea is to establish practical research institutes to focus on a specific issue for a limited time, usually seven years.

“The CRCs are probably the biggest investment that the Australian government

Flu busters: work by Peter Colman (left), Jenny McKimm-Breschkin and Jose Varghese on the structure of the protein neuraminidase led to the influenza drug Relenza.



has made in encouraging commercialization in the life sciences,” says Beryl Morris, chief executive of Vaccine Solutions, which itself was spun out of the CRC for Vaccine Technology. “The rewards are coming, not just in commercialization, but also by developing a greater pool of people who understand how to take science into the mainstream economy.”

The main problem with the CRCs, however, is that they don’t take discoveries far enough along the development pipeline to attract interest from large pharmaceutical companies and, just like other research groups, technology continues to be spun out into small companies that need intermediary funding. “Australian biotech is good at spawning new companies. But bridging to

commercialization — getting a deal done with a big pharmaceutical company — is a competency we don’t have,” says Peter Molloy, chief executive of Biota, based in Melbourne and one of the few Australian companies to shepherd a drug onto the world market (see ‘From wool to flu remedy’).

Australia’s venture-capital markets may be immature compared with other regions,

From wool to flu remedy

The unusual tale of how wool research led to the influenza drug Relenza is a classic illustration of how Australia’s strength in rural research underpins the nation’s growth in biotechnology. But it is also a story that highlights some of the pitfalls to avoid when commercializing research.

Within 50 years of European settlement in 1788, sheep were grazing in every colony of Australia. The annual wool clip was more than two million kilograms and wool had become the nation’s main export. But in the 1950s, the wool industry was threatened by the development of nylon, a reliable synthetic fibre with predictable properties. In response, the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia’s largest science organization, launched a counterattack involving research into every aspect of wool — from breeding sheep for finer wool to understanding the physical and chemical properties of individual fibres.

To investigate protein structure, the researchers turned to X-ray crystallography — invented by Anglo-Australian Nobel laureates William and Lawrence Bragg. The impact was profound — it improved dyeing and stopped wool from yellowing and shrinking in the wash. But a downturn in the wool industry in the 1970s encouraged protein chemists at the CSIRO to shift their focus away from wool and link up with their colleagues in medical research.

Targeting flu

In the 1950s, medical researchers at the Walter and Eliza Hall Institute in Melbourne discovered that the influenza virus carries enzymes known as neuraminidases, which help it to enter cells. Inhibiting neuraminidase enzymes became a strategy for treating influenza.

Peter Colman, a researcher at the CSIRO Division of Protein Chemistry, collaborated with a colleague, Jose Varghese, and Graeme Laver at the Australian National University in Canberra to identify the three-dimensional structure of neuraminidase and observe what changes occurred when the influenza virus mutated into a new strain. In 1983, they published their first crude image of the protein (*Nature* **303**, 35–40; 1983).

The work attracted the attention of international drug company Glaxo Wellcome, but a year of negotiation led nowhere. It was too difficult to persuade the company to invest in a small team on the other side of the world.

A local start-up company called Biota came to the rescue and, with government support, the work continued. In the mid-1980s, working with synchrotrons around the world, Colman and Varghese made the long-awaited breakthrough. “It was slow, difficult work, but it showed us that one part of a coat protein didn’t change in the flu strains. There was a cleft in the neuraminidase protein — a potential target for a drug,” says Colman.

The researchers eventually designed a synthetic molecule that could plug this cleft and disrupt the virus’s life cycle. This synthesized molecule became the basis for the drug Relenza, commercialized by Biota in 1999 with GlaxoSmithKline.

But it took longer than anticipated to get the drug through the US Food and Drug Administration’s approval process, and some clinicians have raised concerns about Relenza’s performance. Biota’s shares collapsed in value following the company’s failure to deliver a long-heralded royalty income.

Since then, Biota has survived and learned, as has the wider industry. Colman is now at the Walter and Eliza Hall Institute looking at the structure of the proteins responsible for cell death with a view to developing new anticancer drugs. And Varghese continues at the CSIRO, using synchrotron X-ray diffraction to determine the structure of proteins involved in a range of conditions including diabetes, inflammation diseases and certain cancers.

Woolly end

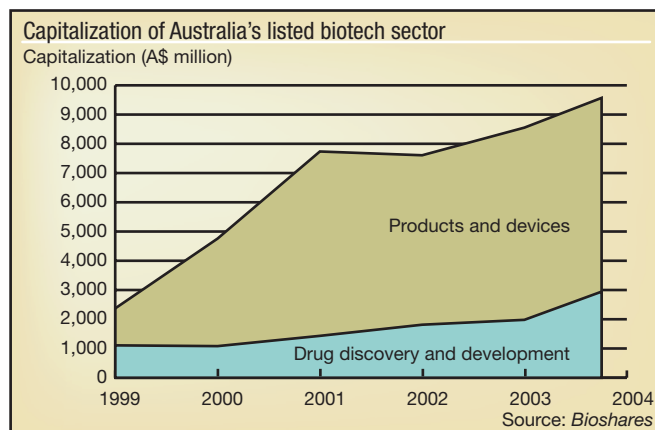
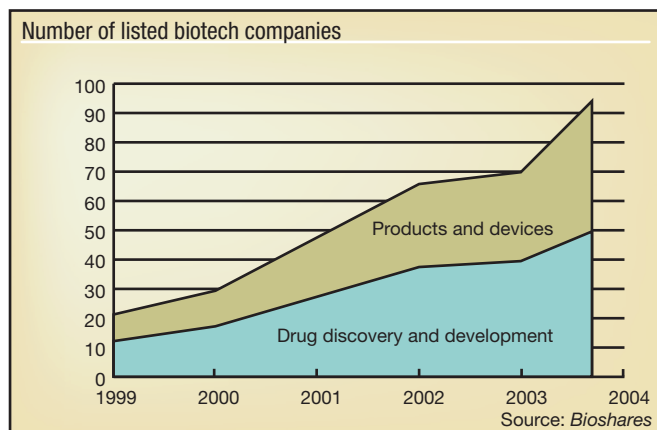
And what of wool? The past half-century of research has helped keep the industry in business, despite synthetic fibres. The latest innovation is a product called Optim. “We found we could transform wool by stretching and setting the fibres to create a new fibre with a silk-like touch, distinctive sheen and subtle lustre, which retains the best properties of wool,” David Phillips from the CSIRO’s Division of Textile Fibre Technology.

“We needed to know exactly what was happening at the molecular level, so we used synchrotron X-ray diffraction at the Photon Factory in Japan. The analysis confirmed that we had succeeded in changing the protein structure of the wool to a structure similar to silk,” says Phillips.

Niall Byrne

Home grown: the sheep and wool industry (left) has been a staple part of Australia’s economy for centuries. Much of this longevity is a result of constant innovation, such as Optim, a silk-like fibre made from wool (right).





Growth industry: in the past five years, Australia's biotechnology sector has begun to assert its authority, with a rise in the number of companies listed on the stock exchange (left) and an increase in capitalization of more than 300% since June 1999.

but they are improving. "There are a lot of biotech companies here, public and private, which suggests there is plenty of money to get things going," Gearing says. But finding enough venture funding to get a programme through to the later stages is difficult. The capital raised in Australia is lower than that raised for equivalent-stage companies in the United States and Europe. In Australia, fundraising rounds of up to A\$5 million are common — A\$50 million is unheard of.

Beames agrees. "It's like pulling teeth," he says. "There is no depth to the venture-capital market." He blames a lack of proven successes — money flows where the returns are greatest, and venture capitalists are not convinced return on investments in Australia will be big enough.

A rising tide

But access to the public market is cheap and easy in Australia, and a flood of small biotech companies have listed on the Australian Stock Exchange (ASX) to raise a few extra million dollars. In 2003 there were nine new biotech listings on the ASX, raising only A\$113 million. So far in 2004, there have been six new listings, raising A\$32 million. Most companies are still in the early stages of product development.

"The ready availability in Australia of stock-exchange listings for companies that are immature by world standards is one of the big negatives of this industry," says Molloy. "The temptation is to list with promises that are difficult to fulfil because of the timelines involved. That leads to a cycle of disappointment that reflects badly on the local industry. It's a real quandary, because the alternative sources of funding are so thin."

But Australian retail investors are not always averse to high-risk investments. "Australia has been historically strong in backing

speculative mining companies. And those investors are happy to look at biotechnology in the same way," says Panaccio.

The institutional support behind the market for Australian mining shares, however, does not yet exist for biotech companies. Most listed companies are too small to interest brokers or institutional investors, and many are so thinly traded that it is pointless for analysts to prepare detailed research reports on the stocks. The result is an inefficient public market. "People have real difficulty valuing these companies," explains Beames.

Industry insiders are quick to admit that the sector lacks commercialization skills. "There are few people in the Australian biotech sector with experience on both sides of the table," says Molloy. But this is changing. More companies are making partnership deals with global pharmaceutical companies or pushing discoveries closer to a commercial stage.

"I'm optimistic about it," Gearing says. "Products are moving up the pipeline all the time. Many are getting close to some nice deals where royalties will start to flow."

Learning curve

But Biota's experience with its influenza drug Relenza highlights some of the potential problems that can occur with the partnering model. The company's partnership with GlaxoSmithKline (GSK) is yet to produce a reasonable royalty stream, ten years after the deal was signed. Its failure hangs over the Australian industry like a dark cloud.

"There are many forces at play that influence the way big pharmaceutical companies make decisions, and I don't think that we fully understand those yet," says Molloy. Australia, it seems, is still out of its depth in the global commercialization of its science.

Still, there is a clear sense of optimism in the industry, a feeling that the widespread entrepreneurialism and the buzz of activity at pre-commercialization stages will soon blossom into a flourishing commercial biotech sector (see graphs and table).

Beames, who returned to Australia after a decade in the biotechnology industry in the United States and Britain, says that the gaps in commercialization skills will be filled, at least partly, from overseas. "While the

Australia's top ten biotech companies (April 2004)

1. CSL	3,991
2. Novogen	612
3. Peptech	256
4. Metabolic Pharmaceuticals	179
5. Genetic Technologies	129
6. pSiVida	121
7. Progen Industries	117
8. Amrad	92
9. Starpharma	88
10. Epitan	83

(ranked by market capitalization in A\$ million)

Excludes investment companies

Source: Bioshares



David Beames believes that successive Australian governments have displayed an aversion to picking winners.



industry stays small, it can't grow from within. We're relying on Australians coming back," he says. "America is a wonderful place to work, but it's hard to beat Australia as a place to live and bring up children."

And Baghai points out that not all of Australia's biotech industry is reliant on the massive capital injections needed for drug commercialization. Many service companies have sprung up around more conventional business models. "For example, Australia is extremely good at instrumentation," he says. "That has a different economic structure —

building a great product, pricing it correctly, servicing it. There are financial and capital issues with competing with the United States on drug discovery, but the structure of these other businesses means that Australia has a better chance to compete."

Australia's biotech industry is changing fast. "If you wind forward two or three years, the sector will look significantly different," Gearing says. "Many companies will have got compounds through the phase II hurdle and will have signed up major royalty-based deals with big drug firms."

Merger activity is widely anticipated among the many small listed biotech companies. "I think there will be a period of merger and acquisition activity that will consolidate the industry," says Greg Collier, chief executive of AGT Biosciences, a Victorian company interested in using gene discovery to identify therapies for conditions such as diabetes and depression. "There are many small companies out there that probably shouldn't be, and they will have to merge to be successful in the long term." AGT itself plans to merge with a private Californian research company called ChemGenex Therapeutics.

Lack of commercialization experience is not expected to hold Australian biotech back for long. "There are several young managers who may not be as experienced as their American counterparts, but they are perhaps a bit more adventurous and flexible," says Beames. "It's an exciting time. It's just a pity that it is so frustrating at the capital end of things."

One thing that most Australian biotech managers agree on is the need for a success story to lift the industry's profile and attract capital. "The challenge for Australia is to build companies with critical mass," Panaccio says. "If we generate a few success stories and build companies that can raise A\$50 million or A\$100 million and take on big projects, then I think we can have a vibrant industry. Success drives success."

The industry is on the edge of great things, according to Molloy. "I absolutely believe that we need one good success story," he says. "Relenza was hopefully going to be that. It turned out not to be. I think there's still great potential for that success story to come out of the Australian industry." ■

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Is the future of agriculture in biopharming, an industry that uses modified crops to grow pharmaceuticals or foods with enhanced health benefits? Brad Collis investigates how the Australian industry is carving out a niche for itself.

Farmers to pharma

Met Lawrence Richmond, a fourth-generation woolgrower from Victoria's Western District, an area which for 150 years has been the centre of Australia's traditional, and once most wealthy, industry — sheep.

But for Richmond, such tradition means nothing. He has become an agrarian revolutionary, ripping out the fences that once penned his prized merino sheep to give his new combine harvesters unfettered access to a new horizon.

In his mind, the golden fleece has been supplanted by golden ears of wheat and barley. And Richmond is now preparing for his own metamorphosis from farmer to pharma — from growing sheep to producing pharmaceuticals.

Grain revolution

In March 2004, the Australian grains industry unveiled a 25-year strategic plan to transform itself into a competitive biopharming sector. It was the product of extensive research, which included interviews with national and overseas users of grain, and with multinational chemical and pharmaceutical companies.

The key element, hotly debated among growers, is a recommendation to loosen the reliance on traditional commodity markets — which are being strongly challenged by emerging exporters such as India, China and former Soviet republics — and to concentrate instead on becoming a leader in new grains-based products.

If this plan is realized, a field of wheat in Australia won't be simply one staple crop. Instead it will be a vast assembly of tens of thousands of leafy biological factories

producing the molecular ingredients for foods, pharmaceuticals, nutraceuticals and even natural chemical compounds for processing into biofuels, plastics and other functional products.

Australian industry projections put the earnings of the new products based on plant biotechnology at five times the current grain harvest. Significantly, this can be achieved with existing, or even less, land and water resources — critical issues for Australian farmers, especially in drought years.

That is why the grains industry — on the advice of the Grains Research and Development Corporation, a statutory body financed by growers — is tying its future to advances in biotechnology. It is also why the industry is attracting newcomers such as Richmond, whose once sacrosanct pastures are making way for customized crops.

This is not a distant vision. Already Australian farmers are, for example, growing different buckwheats to the precise instructions of individual Japanese restaurants, and barley varieties with exacting specifications for international brewers. Australian plant breeders have also bred specific durum wheat varieties, with high gluten quality and a yellow colouring, for Italian pasta manufacturers. A number of biopharming trials are already under way.

Filling a niche

The Australian industry is still a small player in biopharming compared with the overseas multinational companies that dominate the market. "Internationally we are seeing major investment in the area by Nestlé, Unilever and other food giants, and also by venture capitalists — including

Burrill and Company, Lombard Odier and Spencer Trask," says grains-industry consultant Graeme Polknee, based in Melbourne, and a co-author of the 25-year plan.

Canadian, US and European researchers are also exploring new plant biotechnologies, although their focus is on developing alternatives to fossil fuels. Corporations are mindful of the looming high penalties for companies that generate carbon emissions. Dow Chemical and Cargill have invested US\$300 million in a joint-venture biorefinery in Nebraska to produce plastic package wraps and textile fibres from maize and bacteria, and the European Union has production targets for biofuels.

But there is untapped potential in specialized markets for Australia to match the global demands for therapeutic, pharmaceutical and medical products with the nation's unique growing conditions and seed technology. "Our larger competitors will probably focus on large-scale products, leaving niche markets open to Australia," says Polknee.

One particularly enticing prospect is a collaboration with major agricultural customers such as China. "The Chinese have a strong interest in functional foods to tackle a growing epidemic of obesity and diabetes. And several Australian companies are working with Chinese partners on biodegradable plastics based on grains," says Polknee.

Another niche area is the production of specialized feed for cattle, pigs, chicken and fish that enable the animals to produce pharmaceutical compounds such as leukaemia drugs, and beneficial foods that treat or improve teeth and gum disorders. Australia has the soil, the climate and the technology to capitalize on these high-value applications.



Australian grain grower Lawrence Richmond plans to grow pharmaceuticals.



BRAD COLLIS

Last year a Cooperative Research Centre (CRC) for Innovative Grain Food Products was established as a driver for change. Under Australia's CRC scheme, focused research programmes are set up as joint ventures between government, universities and industry for a limited time, usually seven years.

The new grain CRC is the first to be established nationally as an overtly commercial enterprise, with major investors including the food companies Joe White Maltings, Danisco Australia and Weston Technologies (a subsidiary of European food giant Associated British Foods). This mix of corporate, government and university

Graeme McMaster: turning grains into nutraceuticals and pharmaceuticals.

investors has supplied A\$100 million (US\$70 million) in start-up funds. Their aim is to create a new A\$40-billion grains-based manufacturing sector in Australia in two decades.

Wavering governments slow progress on GM

In a setback for Australian biotechnology — one that is driven more by marketing pressures than by scientific or ethical considerations — most state governments have introduced moratoria on the commercial planting of genetically modified (GM) food crops.

But it was the Victorian state government's March 2004 decision that took the industry by surprise, given that state's substantial investment in biotechnology.

State Premier Steve Bracks announced a four-year moratorium on GM canola saying: "The state government has a responsibility to consider market implications for our exporters". And in May, Monsanto cancelled its efforts to grow GM canola in Australia.

Australia's take on GM foods is fundamentally different from the United States and Europe, where the issue is driven by domestic markets. In contrast, Australia's farmers export 80% of their produce, with the sector earning more than A\$26 billion (US\$18 billion) in 2004.

Grain and dairy exporters have found that many of their Asian customers are not yet comfortable with the prospect of GM products entering their food chain.

Many biotechnologists were disappointed by the government's decision and fear that its

impact could spread well beyond the grain industry. Australia's dairy farmers, for instance, have invested heavily in GM-based research on livestock, pastures and products. Some dairy leaders may start to question that strategy if it looks as though there will be no market for the products.

Plant breeders are getting smarter at avoiding the GM food debate by applying modern 'conventional' techniques.

"First, we have molecular markers closely linked to many important traits in the breeding programmes. Second, we have tools that allow marker scanning of the whole genome. Third, through association mapping projects, we have or are developing whole-genome fingerprints for many key lines and important varieties of wheat and barley," says Peter Langridge from the Australian Centre for Plant Functional Genomics at the University of Adelaide.

These techniques are proving useful in introducing desirable traits. Drought-tolerance from the wild grasses, which grow in the harsh climes of central Asia and the Middle East, has been transferred to modern Australian wheats. Although faster than manual pollination and back-crossing, these processes are still excruciatingly slow compared with gene modification.

There is an undercurrent of dissent among Australian plant biotechnologists, who feel thwarted by the media debate that preceded the moratoria, despite the federal government approving commercial trials of GM crops.

The public debate has centred on herbicide-resistant varieties of canola manufactured by Monsanto and Bayer. And it has been used by lobby groups to stir public unease about global companies supposedly controlling food supplies.

These examples have many plant biotechnologists worried that the anti-GM mood is becoming anti-science and that this, more than commercial constraints, is the industry's greatest obstacle.

Despite the setback, Paul Donnelly, the director of the Cooperative Research Centre for Innovative Dairy Products — a collaborative programme between government and industry — is optimistic about the future of GM foods in Australia. "I think we need to encourage the community and markets to consider individual applications of GM products on their merits," he says. "When we start to see GM applications, which bring clear medical, environmental and community benefits, I think the community perception of the role of GM in agriculture will shift."

Niall Byrne

“Other countries with large areas of arable land are catching up with us,” says the CRC’s managing director, Graham McMaster. “Using biotechnology to move to new food, health and industrial products can keep us ahead of changing trading conditions by going down a whole new road and becoming the leader in new markets.”

Underpinning this ambition is Australia’s leading-edge research into the use of plant biotechnologies to develop customized products. Using these gene technologies for new products also takes the industry much further than the conventional applications of biotechnology for inbuilt pest and disease resistance.

To date, this hasn’t required direct genetic modification, involving introducing or

The dairy industry is planning for a future that includes cloned and transgenic cows.



VICCI CROWLEY-CLOUGH

modifying genetic material. It does, however, rely heavily on other gene technologies — such as molecular markers, which allow breeders to quickly identify and select seedlings with useful traits. Another

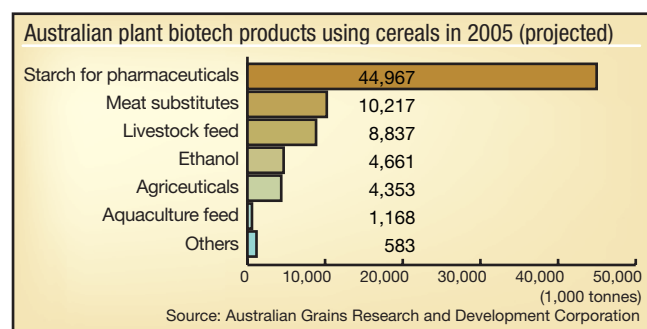
approach is double-haploid production, in which the genetic material of pollen containing desirable traits is duplicated to form new plants. This circumvents the need for fertilization and accelerates the transfer of genetic discoveries into new crop varieties.

Scientists from the CSIRO are using a ‘gene silencing’ technology to produce healthier cooking oils and margarines from grains. This is not gene modification. It works by using natural plant mechanisms to simply ‘switch off’ the genes that convert oleic acid into cholesterol-raising fatty acids. It is the development of advanced gene technologies that the Australian grains industry hopes will give it a leading edge in the world agricultural market.

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Towards a Single Vision for the Australian Grains Industry — 2005–2025

► www.grdc.com.au/bookshop/docs/strategic_plan1.pdf



Biotech companies are exploring Australia's unique ecosystems in search of novel compounds for the next generation of pharmaceuticals and chemical agents. David Blake profiles the companies built on Australia's biodiversity.

Biodiscovery – from reef to outback

PORT DOUGLAS DAINTREE TOURISM ASSOCIATION

Drug developers are increasingly looking to nature for inspiration, and with good reason. "Nature is a better chemist than any person. Organisms don't produce compounds for the hell of it. Chemists do!" says Matthijs Smith, vice-president, technology and corporate development, at Melbourne-based Cerylid Biosciences.

Australia's millions of years of isolation have given rise to a unique flora and fauna that includes 10% of the world's plant and animal species. Although the headline acts, such as koalas and kangaroos, might interest tourists, it is the marine organisms, insects, plants and microbes that have captured the attention of Australia's bioprospectors. The creatures of the Great Barrier Reef have, for example, developed some of the world's most potent toxins; and a hectare of the 135-million-year-old Daintree rainforest contains more flowering plant species than the whole of North America.

Australia took an early lead in setting up research programmes and companies focused on natural-product drug discovery. The Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia's largest national research body, did a lot of the initial work in the 1940s and 1950s. "Not of the sort we do today, which involves high-throughput screening, but a lot of isolation of alkaloids and biologically active compounds," says Ian Jenkins, deputy director of the natural-product discovery unit at Griffith University in Brisbane.

Spoilt for choice

Australia's biodiversity reflects its geographical diversity. "We have exceptionally diverse ecosystems. You have mega-diverse tropical ecosystems in the north, temperate forests in the south, and desert regions in central Australia, coupled with the biggest reef system on the planet, off-shore," says Roger Drinkwater, research director of Xenome, a natural-product discovery company based in Brisbane.



Some companies and research centres have been established to systematically screen for novel bioactive compounds; others take their lead from observations of the natural world. No single organization leads the way, but companies such as Xenome, Cerylid Biosciences, Biosignal (Sydney), Entocism (Canberra) and Toxitech (Townsville) form the backbone of a vibrant discovery sector. These are joined by the Townsville-based Australian Institute of Marine Science, which supplies the US National Cancer Institute (NCI) in Bethesda, Maryland, with up to 5,000 extracts a year from marine organisms.

Another group, including Novogen (Sydney), Peplin Biotech (Brisbane) and Solbec Pharmaceuticals (Perth), see themselves as drug developers working downstream of the discovery sector, tailoring pharmaceutical products from lead compounds.

Xenome is one of only two companies in the world developing drugs based on the toxins produced by reef-dwelling cone shells. These poisonous marine snails, found along Australia's northern coastline, are veritable factories for producing pharmacologically diverse venom peptides. Such peptides have traditionally attracted drug researchers, because they offer possibilities for controlling nerves, are valuable as biological probes, and can potentially be used for treating intractable pain, urinary incontinence, stroke, epilepsy, anxiety and high blood pressure. The company, a spin-off from snake venom research at the University of Queensland in Brisbane, is close to starting clinical trials of its compound XEN-2174 as a pain treatment.

Cerylid Biosciences is working on new therapeutics derived from natural products. Its lead product, CBL-316, is an extract from the bark of a rainforest tree of the *Agelia* genus from Sarawak in Malaysia. This agent contains a previously unreported structural feature, and its mode of action seems to be distinct from other compounds identified to



Cone shells (*Conus* sp.) hunt with a harpoon loaded with a cocktail of venom peptides that attack the nervous system. Australian and international companies are investigating these peptides for treating conditions such as pain, stroke and epilepsy.

date. In studies conducted by the NCI, CBL-316 demonstrated activity against melanoma, breast- and lung-cancer cell lines. The compound enters a phase I cancer trial in 2005.

The company traces its origins to the Melbourne-based drug developer Amrad, which ran a natural-products discovery division for many years. Changing business plans and funding constraints forced Cerylid's spin-off in 2000. Among its assets is a library of approximately 650,000 extracts, sourced not only from Australia but also from Papua New Guinea, southeast Asia and even Antarctica. "This gives us exposure to a wide chemical diversity," says Smith.

The library has been used in collaborative screening studies with international drug developers such as Aventis, Chiron and Chugai. It is diverse, with representatives from nine major chemical families.

Australian plants have yielded a number of potential anticancer agents. Novogen is developing analogues of the isoflavones from red clover (*Trifolium pratense*) for evaluation as potential treatments for cancers and cardiovascular disorders. And Peplin Biotech has partnered with Allergan, a pharmaceutical firm based in Irvine, California, to develop a compound derived from the ubiquitous weed *Euphorbia peplus* to treat non-melanocytic skin cancer.

Battling biofilms

Not all natural-product companies focus on human therapeutics. Biosignal in Sydney is developing furanone compounds extracted from the small red seaweed *Delisea pulchra* found along Australia's southeastern coastline. These furanones show great potential as marine antifouling agents and more.

The build-up of plant and animal material on ship hulls is an enormous problem in the

be globally banned as of 2008. So far, there is no obvious replacement.

The potent compounds found in *D. pulchra* were discovered by Peter Steinberg, a marine ecologist at the University of New South Wales in Sydney. He was investigating how algae defend themselves against being smothered by other marine plants and animals. Biosignal's synthetic furanone analogues inhibit the chemical signalling systems that bacteria use to coordinate aggregation into biofilms. The compounds could find application wherever biofilms are a problem — not only in the marine environment but also fighting dental plaque, for example, or dealing with biofilms on catheters or contact lenses.

Untapped potential

Australia's aboriginal people make use of many native plants as medicines — at least 70 species in central Australia alone. A few of these Aboriginal medicines, such as the ubiquitous eucalyptus oil, tea tree oil and emu oil, are widely used, but indigenous knowledge is a largely untapped resource for biodiscovery. Aboriginal medicine is a complex system closely linked to the culture and beliefs of the people and their knowledge of the land and its flora and fauna. Many research groups are hoping to involve and reward the traditional owners in exchange for this knowledge.

Researchers have barely tapped Australia's enormous biodiversity. With at least two million species of animals and plants plus a vast number of microorganisms, it is highly likely that the nation's biodiscovery industry will grow.

David Blake is co-editor of *Bioshares*, a specialist biotech stock report.



Cerylid's library of 650,000 biological extracts.

Biomedical research in Australia may have chalked up some successes, but it has also let some money-spinning ideas slip through its fingers. Having learned its lesson, this nascent industry is now beginning to flex its muscles. David Blake reports.

Gaining medical momentum

DREW BERRY/WEHI

Four letters sum up the how and why of Australian biomedical research as it stands today: GCSF. This abbreviation, which stands for granulocyte colony stimulating factor, will always be known as the one that got away.

Discovered in 1986 by Don Metcalf at Melbourne's Walter and Eliza Hall Institute (WEHI), GCSF is a hormone-like protein that stimulates certain bone marrow cells to make specialized white blood cells. It was patented and commercialized by the California-based biotechnology giant Amgen, and is now routinely used to help patients recover from cancer therapy. Sold under the brand names Neupogen and Neulasta, GCSF has yielded a massive US\$5.7 billion in sales in the past three years alone.

But rather than representing Australia's inability to exploit its discoveries properly, GCSF is a turning point. Some would argue that it had to be taken up by another party and become a huge money-spinner to initiate a sea change in Australian medical research. In the mid-1980s "the world was naive and the sorts of agents we were producing and cloning had no known commercial value", Metcalf recalls. "Pharmaceutical companies were uninterested in growth factors."

Metcalf and the WEHI learned from GCSF. Shortly afterwards a related cytokine, GM-CSF, was successfully patented and the

royalties flowed. GCSF also created the backdrop for Amrad, now a stalwart of the Australian biotech industry. In many ways, Amrad's story represents the sector's story.

Amrad was established by the Victorian state government in 1986 as a vehicle to develop and commercialize technology from four Melbourne-based research institutes, the WEHI (immunology), the Macfarlane Burnet Institute (virology), the Murdoch Childrens Research Institute

and the Howard Florey Institute (brain research).

A survivor

The company went on to expand its partnerships, add extra business activities, list on the Australian Stock Exchange, experience a string of clinical trial failures, divest businesses and go through a 'rough patch'. Surprisingly, it is still in business. But now it is a leaner, cashed-up company with an



ADVANCED LABS



Pete Smith has overseen a change of direction at biotech firm Amrad.

express focus on cytokine biology and drug development, with a market value of about A\$100 million (US\$70 million) and A\$60 million in the bank. Its projects are still dominated by research emanating from the WEHI.

Leading Amrad is Pete Smith, who is typical of the new breed of Australian biotech managers. Formerly a biotech and healthcare analyst for several merchant banks in the United Kingdom, he was also a co-founder of Onvyax, a British immunotherapy firm.

Smith is not the only new recruit for Australian biotech. Numerous companies are headed by returning expats, drawn back to Australia for various reasons, including attractive government incentives, the desire to raise their children in the relaxed antipodean lifestyle, and the challenge of working in a youthful and vibrant industry.

Although the medical-research sector has learned the lessons of GCSF, all is still not perfect. Ian Frazer from University of Queensland — developer of two vaccines against human papilloma virus — believes



that universities still struggle with technology transfer. “There is still a problem with the business models, particularly when things are spun out of universities,” he says. “Universities haven’t learned to let go yet, but that will be resolved as market forces take over and determine how things are allowed to develop.”

For John Stocker, of consulting group Foursight Associates, a major challenge confronting the medical biotech sector in Australia is the paucity of licensing executives who have strong experience in protecting the intellectual property of discoveries and in commercialization. “We need to understand how to extract real value when forging deals. We will probably have to do so by recruitment,” says Stocker.

Another pressing challenge for Australian researchers is to move their work a lot further down the track before contemplating starting a company or even getting the pharmaceutical industry interested, says Peter Colman, head of the WEHI’s Structural Biology Division. Last November, the WEHI opened an A\$27-million biotechnology centre. Its director, Suzanne Cory, expects the new centre to allow researchers to take

their basic-science discoveries further along the research and development pipeline. The centre includes a high-throughput chemical screening facility unique in Australia.

Lack of confidence

Michael Aldridge of Peplin Biotech, a Brisbane-based cancer-drug-development company, notes that players in the local therapeutics industry are not confident that they can create and build a business in Australia. “There’s an expectation or trend to license to Merck, GlaxoSmithKline and Pfizer. There is no recognition that you can license to more focused players, who will provide you with a more collaborative role in the development process,” he says. “There’s also the opportunity to do these things independently and take them to the market yourself. But significantly more resources will have to become available for companies to achieve that.”

However, the recent decision by a Singapore biotech company CyGenics to move to Melbourne may signify a promising new trend. CyGenics grows stem and blood cells to treat AIDS, leukaemia and blood disorders. The company recently announced plans to trial in Melbourne a technology to grow a person’s own stem cells in synthetic bone marrow outside the body.

And Living Cell Technologies — a New Zealand company — recently transferred to Adelaide ahead of a planned listing on the Australian Stock Exchange to fund its development of a cell therapy tool for tissue repair.

These recent events are promising signs that the Australian capital market is starting to deliver the right formula for medical biotechnology. ■

David Blake is co-editor of *Bioshares*, a specialist biotech stock report.



David Boyle and his colleagues turned their work on poultry vaccines into a vector for HIV vaccines (see page A23).

Immunological strengths lead to new vaccines

Ian Frazer represents the cutting edge of vaccine development in Australia. Not only has his research team at the University of Queensland in Brisbane developed a vaccine to stop the spread of human papilloma virus (HPV) — the virus responsible for almost all cases of cervical cancer — but it has also tackled the much harder problem of creating a vaccine to treat the infection.

“Our vaccines are a great example of how to fight disease on several fronts at once,” says Frazer. The preventive vaccine is currently in phase III clinical trials being conducted and funded by GlaxoSmithKline, Merck Sharp Dohme and CSL, and involving 20,000 women. The treatment vaccine is in phase I trials.

“The two vaccines used together have the potential to save millions more lives, decades sooner than using one alone,” says Frazer, a Scot who emigrated to Australia because of its rich heritage in immunology.

He says most vaccine development in Australia can be traced back to Nobel laureate MacFarlane Burnett, who turned research at the Walter and Eliza Hall Institute in Melbourne from virology to immunology in the 1950s.

In the 1940s, Burnett was concerned with the threat of an influenza pandemic, and embarked on a virological investigation that led eventually to the world's first anti-influenza treatment. He then turned to vaccines and immunology. His theory of clonal selection and how we acquire immunological tolerance led to a Nobel prize in 1960. Perhaps more importantly, he mentored a cohort of scientists who went on to become leading immunologists, including Gordon Ada, Ian Gust, Gustav Nossal and Ian McKay.

A young Frank Fenner was recruited by Burnett to work on mousepox. Later he became the foundation professor of the John Curtin School of Medical Research (JCSMR) in Canberra, and then headed the Global Commission for the Certification of Smallpox Eradication. Fenner in turn recruited veterinarian

Peter Doherty who with Rolf Zinkernagel won a Nobel prize for the discovery of the role of cell-mediated immunity in recognizing and destroying virus-infected cells.

The scientific legacy of these pioneers led directly to the invention of Co-X-Gene, a fowlpox vaccine vector, by teams headed by David Boyle of the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Ian Ramshaw of the JCSMR in the 1980s. This vector is now being used for two prototype HIV vaccines — it carries genes from HIV and a human cytokine to cells in the human body with the aim of triggering a directed immune response.

Boyle had been working on poultry vaccines when he realized that his fowlpox vaccine vector had human applications. Today an Australian public-private partnership is completing phase I trials of a preventive vaccine for HIV with funding from the US National Institutes of Health. And Virax, a Melbourne-based biotech company, is developing a treatment vaccine that is commencing phase II trials. Both trials are being managed by the National Centre for HIV Epidemiology and Clinical Research (NCHECR) in Sydney.

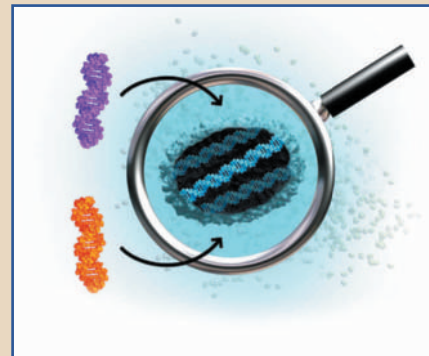
Clinical trials afoot

Today, the Cooperative Research Centre (CRC) for Vaccine Technology has reunited many of Burnett's protégé organizations across the country. Under the CRC's auspices a wide range of vaccines are currently being developed to fight streptococcal infections — a major issue for indigenous communities; Epstein-Barr virus — the cause of glandular fever and nasopharyngeal carcinoma, a particular scourge in China — and cytomegalovirus, a significant cause of birth defects.

“Australia's strengths are in our immunological foundations, and the motivation of our researchers to make a difference in the fight against disease,” says Anne Kelso, director of the Vaccine CRC.

“Malaria research has been an Australian strength for decades. An effective vaccine is urgently needed, as drug-resistant malaria has begun to terrorize Australia's neighbours,” says Beryl Morris, chief executive of Vaccine Solutions, a Brisbane-based vaccine commercialization company. Vaccine Solutions is working with the Vaccine CRC on two of three Australian malaria-vaccine initiatives funded by the Bill and Melinda Gates Foundation.

“No Australian partner has the resources to run a A\$500-million (US\$344-million) phase III trial. So international partnering is still essential. But we have good facilities for early phase trials,” says Kelso.



Directed response: the Co-X-Gene is being used to ferry genes from the AIDS virus and from human cytokines into other human cells in an effort to encourage the immune system to fight back.

“Many small Australian biotechs still take their trials overseas when they could be adding value by doing the trials at home,” says Tony Webber, director of Clinical Network Services, a Brisbane-based clinical-research management company. In fact, most of his work comes from companies in the United States drawn to Australia by a combination of high quality, low prices, a capacity to service tropical, sub-tropical and temperate disease issues, and a regulatory framework respected by the US Food and Drug Administration.

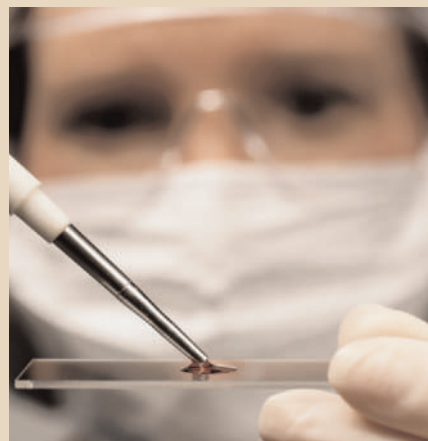
“Australia has developed a special expertise in HIV clinical trials,” says Sean Emery, head of therapeutic and vaccine research at the NCHECR. The Australian government responded to the AIDS crisis with a national strategy that created three research centres devoted to virology, clinical research and social research. That 1990 decision has led to an infrastructure supporting both research and clinical trials. The NCHECR is now coordinating ten major HIV trials across four continents.

Webber says that there has been strong growth in contract clinical trials in recent years. “This is good for Australia's infrastructure, but we need to be sure we can consistently deliver patients for the trials from our relatively small population.”

Emery is more cautious. “The growth in Australia's clinical-trial infrastructure is exciting but it's important that we maintain the academic integrity of the system,” he says.

“Australia's regulatory authorities have the balance between risk and benefit about right,” notes Frazer, although he says there needs to be better public-sector funding for large-scale clinical trials. “We can't rely on commercial trials alone, in determining the most effective ways to use the products of biotechnology in the community,” he says.

Niall Byrne





When Australian biotechnologists sit down to discuss the future of their industry, size is inevitably on the agenda. Australia may be a large country, but its population is just half the size of that of California. Niall Byrne looks at how Australia's small companies could assert themselves, despite being the underdogs.

Future outlook

Business confidence in Australia's biotechnology sector is growing, and many small, energetic biotech companies are now entering Australia's equity markets. Some see these underfunded companies as a weakness in the sector. But it may be these small firms that deliver on the promise of Australian biotechnology.

Many of Australia's research successes have come from small, underfunded research groups — for instance, the discovery of the role of the bacterium *Helicobacter pylori* in stomach ulcers, the development of the world's first bionic ear and the use of lithium to treat bipolar disorder. Perhaps the biotech flagship that investors are looking for will come from small upstarts, such as two Brisbane companies: Benitec, which hopes to treat disease by using gene silencing; or the even smaller Tissue Therapies, which uses natural protein complexes to promote tissue growth.

Close neighbours

In biotechnology, Asia and Australia often find themselves as partners — Australia being a source of ideas and of education, Asia providing the investment and manufacturing expertise to get products onto the market.

For instance, the biopharmaceuticals company Vital Biotech is based in Hong Kong but does its clinical trials and manufacturing in mainland China, and its research in Melbourne. "Australians are very inventive," explains Vital's chairman, Thomas Ko.

Many large Asian drug companies have formed partnerships with small Australian biotech start-ups. Melbourne-based bioprospector Cerylid BioSciences has formed partnerships with two of Japan's big five pharmaceutical firms. They screen Cerylid's library of natural extracts against their targets

Australia must play to its strengths. It has broad biodiversity and a rich research heritage, and there is no doubt that investment over the past century in agricultural and medical research is now paying off for biotechnology. This research base is also contributing to innovation throughout the Asia-Pacific region (see 'Close neighbours').

Australia's state governments have also discovered biotechnology and are competing to build the biggest, brightest laboratories. Highlights include Queensland's Institute for Molecular Bioscience and Victoria's Bio21 Molecular Science and Biotechnology Institute. But many Australian scientists worry that as governments try to pick winners, they are not maintaining their investment in the basic research that has made the nation's science strong.

One of the biggest, and perhaps most contentious, infrastructure initiatives is the

using assays developed by the Australians. In addition, Cerylid is partially funded by Jafco Asia, an arm of Japan's largest venture-capital firm. And Sydney company Proteome Systems has built strong links with the Japanese giants Shimadzu and Itochu.

Australia's strengths in agriculture and medicine have long been a magnet for Asian students. The result has been the creation of multinational Asian networks linked by a common alma mater. One such network is run out of the University of Queensland. It uses molecular markers to develop drought-tolerant varieties of rice, and operates in Thailand, Laos and Cambodia.

As Australian biotechnology matures, the sector will become an increasingly important source of innovation for the region. **Bob Johnstone**

nation's first synchrotron, to be completed in 2007 at a cost of more than A\$200 million (US\$138 million). Some in the science community would rather have seen this money invested in basic research. But Gustav Nossal, former director of the Walter and Eliza Hall Institute in Melbourne, regards it as a "fundamental discovery tool for biotechnology and the next generation of designer drugs".

Australia is already known as a test bed for new technologies — it has a reputation as a nation of early adopters. Parallels are beginning to emerge in the biotechnology sector. Australia is becoming a popular base for translational research, clinical trials, health economics, population-based medicine and regulatory approval.

Will the next one get away?

Australian scientists often talk of 'the ones that got away'. In the 1940s, Australia built CSIRAC, one of the world's first computers. The nation was also an early player in the space race, with regular rocket launches from Woomera in South Australia. Now Australia is a bit player in both fields.

So will the next big invention slip through its fingers? Although Australia's universities remain relatively naive about technology transfer, the environment is beginning to change. National and regional support groups such as Ausbiotech and the BioMelbourne Network are showing increasing skill in promoting and supporting commercialization. PhD students are being rewarded with equity. And governments are investing in microtechnology and the devices that will deliver the next generation of discoveries. The future is looking good for biotechnology in Australia. ■

Niall Byrne is a science and technology writer based in Melbourne, Australia.